## REMARKS

Upon entry of the following amendment, claims 1, 127 – 170 and 205 – 218 are pending, while claims 2 – 126, 171 – 204, 219 and 220 have been cancelled as being drawn to non-elected subject matter. Claims 127, 145 – 147, 149 and 155 – 157 have been amended to remove informalities. These amendments add no new matter.

### THE CLAIM OBJECTIONS

The Examiner has rejected claims 127, 145 – 149 and 155 – 157 because of the use of bullets. Applicants have amended these claims to address the Examiner's objection. Accordingly, Applicants believe that the present rejection is now moot.

### THE 35 U.S.C. §112, SECOND PARAGRAPH REJECTION

The Examiner has rejected claims 127 – 170 under 35 U.S.C. § 112, second paragraph as being indefinite. Specifically, the Examiner has alleged that the term "valence bond" in claims 127 – 135, 152 and 153, the term "ArG1" in claims 137 – 139, 146 and 147, the term "Het1" in claim 137, the term "Het2" in claim 138, and the term "Het3" in claims 139 and 146, are undefined, rendering the formulas indefinite.

*The Term "Valence Bond"*

Applicants traverse. As stated in the M.P.E.P. §2173.02:

> [A] claim term that is not used or defined in the specification ***is not indefinite if the meaning of the claim term is discernible***. *Bancorp Services, L.L.C. v. Hartford Life Ins. Co.*, 359 F.3d 1367, 1372, 69 USPQ2d 1996, 1999-2000 (Fed. Cir. 2004)…

Applicants assert that the term valence bond as used in the Specification and claims 127 – 135, 152 and 153 is a well-known term in the chemical arts. As defined by the McGraw-Hill Encyclopedia of Science and Technology, The McGraw-Hill Companies, Inc., (2005) (http://www.answers.com/topic/valency), a "valence bond" or "valence" is:

> A term *commonly used* by chemists to characterize the combining power of an element for other elements, as measured by the number of bonds to other atoms which one atom of the given element forms upon chemical combination. The term also has come to signify the theory of all the physical and chemical properties of molecules that specially depend on molecular electronic structure.

Thus, Applicants assert that the use of the term "valence bond" does not render the formula indefinite as such language is easily interpreted by a person of ordinary skill in the art. As such, Applicants assert that a person of ordinary skill in the art would be able to interpret the metes and bounds of claims 127 – 135, 152 and 153 so as to understand how to avoid infringement. Accordingly, Applicants respectfully request reconsideration and withdrawal of the present rejection.

*The term "ArG1"*

Applicants traverse. Applicants clearly define the metes and bounds of this term in the Specification as originally filed at pg. 6, lines 19 – 22:

> The term "ArG1" as used herein is intended to include an aryl or arylene radical as applicable, where aryl or arylene are as defined above but limited to phenyl, biphenylyl, naphthyl, anthracenyl, phenanthrenyl, fluorenyl, indenyl, and azulenyl as well as the corresponding divalent radicals.

As such, Applicants assert that a person of ordinary skill in the art would be able to interpret the metes and bounds of claims 137 – 139, 146 and 147. Accordingly, Applicants respectfully request reconsideration and withdrawal of the present rejection.

*The terms "Het1", "Het2", and "Het3"*

Applicants traverse. Applicants clearly define the metes and bounds of these terms in the Specification as originally filed at pg. 6, line 26 through pg. 7, line 19:

> **The term "Het1" as used herein** is intended to include a heteroaryl or heteroarylene radical as applicable, where heteroaryl or heteroarylene are as defined above but limited to furyl, thienyl, pyrrolyl, pyrazolyl, 3-oxopyrazolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5- triazinyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, tetrazolyl, thiadiazinyl, indolyl, isoindolyl, benzofuryl, benzothienyl, indazolyl, benzimidazolyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, purinyl, quinazolinyl, quinolizinyl, quinolinyl, isoquinolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, azepinyl, diazepinyl, acridinyl, thiazolidinyl, 2-thiooxothiazolidinyl, as well as the corrresponding divalent radicals.
> **The term "Het2" as used herein** is intended to include a heteroaryl or heteroarylene radical as applicable, where heteroaryl or heteroarylene are as defined above but limited to furyl, thienyl, pyrrolyl, pyrazolyl, 3-oxopyrazolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5- triazinyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, tetrazolyl, thiadiazinyl, indolyl, isoindolyl, benzofuryl, benzothienyl, benzimidazolyl,

> benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, quinolinyl, isoquinolinyl, quinoxalinyl, carbazolyl, thiazolidinyl, 2-thiooxothiazolidinyl, as well as the corrresponding divalent radicals.
> **The term "Het3" as used herein** is intended to include a heteroaryl or heteroarylene radical as applicable, where heteroaryl or heteroarylene are as defined above but limited to furyl, thienyl, pyrrolyl, pyrazolyl, 3-oxopyrazolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, pyridyl, tetrazolyl, indolyl, isoindolyl, benzofuryl, benzothienyl, benzimidazolyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, quinolyl, isoquinolyl, quinoxalinyl, carbazolyl, thiazolidinyl, 2-thiooxothiazolidinyl, as well as the corrresponding divalent radicals.

As such, Applicants assert that a person of ordinary skill in the art would be able to interpret the metes and bounds of claims 137 – 139, and 146. Accordingly, Applicants respectfully request reconsideration and withdrawal of the present rejection.

**THE 35 U.S.C. §103(A) REJECTIONS**

The Examiner has rejected claims 1, 205 and 213 – 218 under 35 U.S.C. § 103(a) as being unpatentable over Dunn (US Patent No. 5,830,999; "**Dunn**") in view of Franke & Groeneveld (Transit. Met. Chem., 1981, 6, 54-56; "**Franke**"). Specifically, the Examiner has alleged that **Dunn,** while teaching that ligands which bind specifically to the two $His^{B10}Zn^{2+}$ sites in insulin stabilize formulations of insulin hexamers, does not teach the specific zinc ligands of the claimed invention. However, the Examiner continues by stating that **Franke** teaches that tetrazoles can coordinate zinc, and as such the skilled artisan would have been motivated to combine the tetrazole ligands of **Franke** with the insulin hexamers of **Dunn**. Thus, the Examiner has alleged that the invention as a whole is *prima facie* obvious.

Applicants traverse. To establish a *prima facie* case of obviousness, three basic criteria must be met: 1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; 2) there must be a reasonable expectation of success; and 3) the prior art reference (or references when combined) must teach or suggest all the claim limitations. *See e.g.* M.P.E.P. §2143. Furthermore, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *See e.g.* In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Applicants assert that the neither reference implicitly or explicitly teaches or suggests that the tetrazole ligands of **Franke** would be useful to stabilize the insulin hexamers of **Dunn**. In addition, contrary to the statement of the Examiner, the ligands of **Franke** are not functionally equivalent to the ligands of **Dunn**. **Dunn** is directed to the use of organic carboxylates as ligands able to bind to and stabilize the insulin hexamers through zinc binding. In contrast, the ligands of the present invention (and the tetrazoles generally taught by **Franke**) bind to and stabilize insulin through zinc coordination. Emdin *et al*. (Diabetolgia 19, 174-182 (1980) (copy enclosed)) make a distinction between zinc *coordination* and zinc *binding*. Specifically, the first is specific coordination of zinc in the insulin hexamer, holding it together *via* the histidine residues, while zinc binding refers to the more aspecific binding of zinc, mainly to carboxylic acid groups on the surface of the hexamer. Thus, Applicants assert that there is neither a suggestion or motivation in the cited references to combine their teachings, since Dunn teaches ligands directed to zinc *binding* while **Franke** discloses only ligands that are useful for zinc *coordination*, and does not teach or suggest that the disclosed tetrazole compounds would be useful to stabilize insulin. Thus, one skilled in the art would not be motivated to combine the teachings of **Dunn** with the ligands of **Franke** since the ligands disclosed in each reference work differently.

The Examiner has rejected claims 1, 127 – 140, 150 – 153, 155 – 157, 205 and 213 – 218 under 35 U.S.C. § 103(a) as being unpatentable over Dunn (US Patent No. 5,830,999; "**Dunn**") in view of Franke & Groeneveld (Transit. Met. Chem., 1981, 6, 54-56; "**Franke**") and Ciarkowski *et al*. (Org. Mag. Res., 1979, 12, 631 -636; "**Ciarkowski**"). The Examiner characterized both **Dunn** and **Franke** as in the previous rejection, and added that **Ciarkowski** teaches specific tetrazole compounds that are functionally equivalent to the ligands of **Dunn**. Thus, the Examiner has alleged that the invention as a whole is *prima facie* obvious

Applicants disagree. Both **Dunn** and **Franke** are discussed above. **Ciarkowski** does not cure the deficiencies of these references as discussed above. **Ciarkowski** merely discloses examples of tetrazole ligands. **Ciarkowski** does not contain either a suggestion or provide motivation to combine its teachings with that of **Dunn**. Thus, one skilled in the art would not be motivated to combine the teachings of **Dunn** with the ligands of **Ciarkowski** since the ligands disclosed in each reference work differently.

The Examiner has rejected claims 1, 127 – 140, 150 – 153, 155 – 157, 205 and 213 – 218 under 35 U.S.C. § 103(a) as being unpatentable over Dunn (US Patent No. 5,830,999; "**Dunn**") in view of Franke & Groeneveld (Transit. Met. Chem., 1981, 6, 54-56; "**Franke**") and Makovec *et al.* (J. Med. Chem., 1992, 35, 3633-3640; "**Makovec**"). The Examiner characterized both **Dunn** and **Franke** as in the previous rejection, and added that **Makovec** teaches specific tetrazole compounds that are functionally equivalent to the ligands of **Dunn**. Thus, the Examiner has alleged that the invention as a whole is *prima facie* obvious

Applicants disagree. Both **Dunn** and **Franke** are discussed above. **Makovec** does not cure the deficiencies of these references as discussed above. **Makovec** merely discloses examples of tetrazole ligands. **Makovec** does not contain either a suggestion or provide motivation to combine its teachings with that of **Dunn**. Thus, one skilled in the art would not be motivated to combine the teachings of **Dunn** with the ligands of **Makovec** since the ligands disclosed in each reference work differently.

The Examiner has rejected claims 1, 127 – 170, 205 – 218 under 35 U.S.C. § 103(a) as being unpatentable over Dunn (US Patent No. 5,830,999; "**Dunn**") in view of Olsen *et al.* (US Patent Application No. 2003/0229120; "**Olsen**"). The Examiner characterized **Dunn** as in the previous rejection, and added that **Olsen** teaches novel ligands for the $His^{B10}Zn^{2+}$ sites of the R-state insulin hexamer that are capable of prolonging the action of insulin. Thus, the Examiner has alleged that the invention as a whole is *prima facie* obvious

Applicants disagree. **Dunn** is as characterized above; namely that it teaches the use of organic carboxylates as ligands able to bind to and stabilize the insulin hexamers through zinc binding. **Olsen is directed to and teaches** insulin preparations where compounds which binds to the Zn site, have been extended with charged groups in order to achieve precipitations resulting in a protracted effect of the insulin, i.e changing of the timing of the preparation. In contrast, the present invention is directed to pharmaceutical compositions whereby the stabilization is improved using zinc binding ligands, but without changing the timing of insulin preparations. As such, the compounds disclosed in Olsen differ from those of the present Application because those in Olsen are extended with charged groups which have been synthesised further. Thus, Applicants assert that

the prior art references, when combined, do not teach or suggest all the claim limitations of the present invention.

In light of the arguments above, Applicants respectfully request reconsideration and withdrawal of the present rejections under 35 U.S.C. §103(a).

**THE DOUBLE PATENTING REJECTIONS**

The Examiner has provisionally rejected claims 1, 127 – 170, 205 – 218 on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims of copending US Patent Application No. 11/226,870.

Upon notification of allowable subject matter, Applicants will file a terminal disclaimer as is appropriate. Accordingly, Applicants believe that the present rejection is now moot.

## CONCLUSION

In view of the above, it is respectfully submitted that the application is now in condition for allowance and issue. Early action to that end is respectfully requested. Applicants believe that no additional fees are due. However, should any fees be due, the Commissioner is hereby authorized to charge any fees in connection with this application and to credit any overpayments to Deposit Account No. 14-1447. The Examiner is invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

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